



Diabetes Mellitus and Site-specific Colorectal Cancer Risk in Korea: A Case-control Study

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Objectives: Previous large-scale cohort studies conducted in Korea have found a positive association between diabetes mellitus (DM) and colorectal cancer (CRC) in men only, in contrast to studies of other populations that have found significant associations in both men and women.

Methods: A total of 1070 CRC cases and 2775 controls were recruited from the National Cancer Center, Korea between August 2010 and June 2013. Self-reported DM history and the duration of DM were compared between cases and controls. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by binary and polytomous logistic regression models.

Results: DM was associated with an elevated risk of CRC in both men (OR, 1.47; 95% CI, 1.13 to 1.90) and women (OR, 1.92; 95% CI, 1.24 to 2.98). This association remained when we controlled for age, body mass index, alcohol consumption, and physical activity level. In sub-site analyses, DM was associated with distal colon cancer risk in both men (multivariate OR, 2.04; 95% CI, 1.39 to 3.00) and women (multivariate ORs, 1.99; 95% CI, 1.05 to 3.79), while DM was only associated with rectal cancer risk in women (multivariate OR, 2.05; 95% CI, 1.10 to 3.82). No significant association was found between DM and proximal colon cancer risk in either men (multivariate OR, 1.45; 95% CI, 0.88 to 2.41) or women (multivariate OR, 1.79; 95% CI, 0.78 to 4.08).

Conclusions: Overall, DM was associated with an increased risk of CRC in Koreans. However, potential over-estimation of the ORs should be considered due to potential biases from the case-control design.

Key words: Diabetes mellitus, Colorectal neoplasms, Colonic neoplasms

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INTRODUCTION

According to the Korean Central Cancer Registry, colorectal cancer (CRC) is the third most common cancer in Korea, and the burden of CRC is rapidly increasing [1]. As the prevalence of diabetes mellitus (DM) in the Korean population has increased, it has become a major cause of morbidity and mortality in Korea [2]. It has been well established that diabetes is an independent risk factor for cardiovascular diseases in both men and women [3]. According to a recent meta-analysis, DM is also associated

with a higher risk of gastric [4], lung [5], liver [6], pancreas [6], and breast cancer [7], but insufficient evidence exists regarding prostate cancer [8]. A history of DM has generally been associated with an elevated risk of colorectal cancer. A potential biological mechanism for increased CRC risk among individuals with DM is that hyperinsulinemia following insulin resistance affects colorectal epithelial cell proliferation, possibly having a tumorigenic effect [9]. Additionally, the overexpression of insulin receptors can affect colon tumorigenesis in DM patients [10]. Larsson et al. [11] found that diabetes was associated with an increased risk of CRC in both men and women in their meta-analysis. Two recent meta-analyses also reported a positive association between DM and CRC risk in both men and women [12,13]. In Korea, three reports have been published on the association between DM and colorectal polyps [14-16]. However, limited data are available regarding CRC in the Korean population. Two large-scale cohort studies have been conducted in Korea, and both studies showed a positive association between DM and CRC in men only [17,18]. Thus, additional epidemiologic studies are needed to assess the relationship between DM and CRC.

In order to clarify the effect of diabetes on CRC risk according to gender and cancer sub-site, we conducted a hospital-based case-control study with 1070 colorectal cases and 2775 controls.

METHODS

Study Participants

We contacted newly diagnosed CRC patients when they were admitted to the Center for Colorectal Cancer, National Cancer Center, Korea between August 2010 and June 2013. We contacted 1259 of the 1427 eligible patients, and 1070 patients agreed to participate in the study and provided informed consent. We selected controls from subjects who visited the same hospital for a health screening program administered by the National Health Insurance Service, which provided insurance coverage to approximately 98% of the Korean population [19] during the period from March 2010 to November 2013. A total of 5936 participants completed a lifestyle questionnaire and a food frequency questionnaire. We excluded participants with inappropriate calorie intake (≤ 500 kcal/d or ≥ 4000 kcal/d, $n=9$) from the analysis. From the remaining 5927 participants, 2775 were age-matched (at five-year intervals) and gender-matched at a 1:3 ratio with 925 CRC patients who com-

pleted a food frequency questionnaire. In addition, 145 CRC cases who did not a complete food frequency questionnaire were included in the current analysis. Therefore, a total of 3845 subjects (1070 cases and 2775 controls) were included in the analysis. In this study, we defined the proximal colon as including the cecum, ascending colon, hepatic flexure, transverse colon, and splenic flexure; the distal colon as including the descending colon, sigmoid-descending colon junction, and sigmoid colon; and the rectum as including the rectosigmoid colon and the rectum. All participants provided written informed consent to participate, and the study protocol was approved by the institutional review board (IRB) of the National Cancer Center (IRB no. NCCNCS-10-350).

Data Collection

The study participants answered questions about their age, marital status, education level, cigarette smoking and alcohol drinking habits, intake of charred meat, household income, regular exercise status, and family history of cancer, and the survey was administered by trained interviewers using a structured questionnaire. In cases, the patient's height and weight were measured before surgery, and in controls they were measured during a health examination. The body mass index (BMI) was calculated by dividing weight by height squared and categorized as underweight (BMI < 18 kg/m²), normal (BMI 18 to 24.9 kg/m²), and overweight (BMI ≥ 25 kg/m²). Engaging in regular exercise was defined as a positive response to the question "Do you exercise regularly?" DM status was defined on the basis of a self-report. Participants were asked if a physician had ever told them that they had DM and what age they were diagnosed.

Statistical Analysis

Categorical data are presented as actual numbers and percentages. The *p*-values were calculated using the chi-square test and the Cochran-Mantel-Haenszel chi-square test with adjustments for age.

The association between DM and CRC was evaluated using binary logistic regression and polytomous logistic regression. The multivariate analysis included covariates that changed the odds ratio (OR) more than 10% compared to the corresponding reduced model.

In order to deal with missing data in covariates, we created a dummy variable for the missing category and included such dummy variables as covariates in the multivariate logistic re-

gression.

All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Table 1 shows the general characteristics of study subjects according to gender. Among men, significant differences were found between cases and controls in age, marital status, education level, household income, BMI, alcohol consumption, regular exercise, family history of cancer, and family history of colorectal cancer. In women, significant differences were found between cases and controls in marital status, educational level, household income, BMI, smoking status, regular exercise, and family history of cancer.

In men, 15.7% of CRC cases (113/721) reported a history of diabetes, compared with 9.8% of controls (184/1878). In women, 11.5% of CRC cases (40/349) reported a history of diabetes, compared with 5.9% of controls (53/897).

The multivariate ORs for the association between DM and CRC were 1.50 (95% confidence interval [CI], 1.15 to 1.97) and 1.97 (95% CI, 1.23 to 3.17) for men and women, respectively (Table 2).

We also conducted sub-site analyses. In men, a history of diabetes was associated with an increased risk of distal colon cancer (multivariate OR, 2.04; 95% CI, 1.39 to 3.00) but was not associated with a risk of proximal colon cancer (multivariate OR, 1.45; 95% CI, 0.88 to 2.41) or rectal cancer (multivariate OR, 1.23; 95% CI, 0.87 to 1.76). In women, a history of diabetes was associated with an increased risk of distal colon cancer (multivariate OR, 1.99; 95% CI, 1.05 to 3.79) and rectal cancer (multivariate OR, 2.05; 95% CI, 1.10 to 3.82) but was not associated with a risk of proximal colon cancer (multivariate OR, 1.79; 95% CI, 0.78 to 4.08) (Table 2). In men, the adjusted OR for subjects with a duration of DM of 10 years or longer was similar to that of subjects who had a history of DM for less than 10 years. However, in women, subjects with a duration of DM of less than 10 years exhibited the highest adjusted OR (Table 3).

DISCUSSION

In this study, DM was significantly associated with an increased risk of CRC in both men and women, and this association remained present after adjusting for age, BMI, charred meat consumption, alcohol consumption, and physical activi-

ty. Previous studies have also found an association between CRC risk and DM status. Larsson et al. [11] reported that DM was associated with CRC risk in both men and women in their meta-analysis. In more recent meta-analyses, this association remained unchanged [12,13]. In Korea, several studies have found a relationship between DM and colorectal polyps [14-16]. However, to our knowledge, only two studies have investigated the association between DM and CRC risk in Korea. Jee et al. [17] conducted a prospective cohort study, finding that DM status was only associated with CRC risk in men. Another prospective cohort study conducted by Shin et al. [18] likewise found a significant association between CRC risk and a fasting glucose level of 126 mg/dL or more only in men. In order to explain the association between DM and CRC risk, a hypothesis involving hyperinsulinemia has been proposed [20]. According to this hypothesis, individuals with DM do not use insulin properly, which manifests as insulin resistance. This leads to a chronic hyperinsulinemic state and the elevation of insulin-like growth factor -1 levels, which then play a crucial role in the proliferation of cells and, finally, the occurrence of CRC [19,20]. In addition to the hyperinsulinemia hypothesis, elevated insulin receptor protein expression in colonic tumors has been proposed as a possible biological mechanism for colonic tumorigenesis because *in vivo* studies have shown that insulin receptors contribute to cell transformation [10].

Interestingly, DM was associated with overall CRC risk, but the association depended upon gender and the sub-site of the lesion. In our study, woman DM patients showed a stronger association than man DM patients with overall CRC risk. However, the *p*-value for the interaction did not indicate statistical significance. Recent meta-analyses have focused on gender-specific differences in diabetes and CRC risk. Wu et al. [21] found that men showed a stronger association between DM and colon cancer, while other studies have found a very similar association among men and women [22,23]. A hormonal difference between men and women has been suggested as an explanation of gender discrepancies, but no consistent effect of gender hormones on CRC incidence has been found. Gunter et al. [24] conducted a case-cohort study and found that endogenous estradiol was associated with an increased risk of colorectal cancer. Additionally, several *in vitro* studies have supported the mitogenic effect of estrogen on large intestine cells [25,26]. However, some studies have reported that estrogen may have a protective function against serious outcomes of hyperinsulinemia [27,28].

Table 1. General characteristics of study subjects

	Men (n=2599)			Women (n=1246)		
	Colorectal cancer (n=721)	Control (n=1878)	p-value ¹	Colorectal cancer (n=349)	Control (n=897)	p-value ¹
Age (y)	58.9±10.1	55.2±8.2	<0.01	57.0±10.2	55.0±9.7	<0.01
<49	130 (18.0)	461 (24.7)	<0.01	87 (24.9)	249 (27.8)	0.06
50-59	233 (32.3)	815 (43.6)		114 (32.7)	333 (37.1)	
≥60	358 (49.7)	596 (31.7)		148 (42.4)	315 (35.1)	
History of diabetes mellitus						
Yes	113 (15.7)	184 (9.8)	<0.01	40 (11.5)	53 (5.9)	<0.01
No	608 (84.3)	1694 (90.2)		309 (88.5)	844 (94.1)	
Duration of diabetes mellitus (y)			0.38			0.79
<4	40 (38.8)	73(47.0)		16 (47.1)	14 (38.9)	
5-9	29 (28.2)	41(26.5)		8 (23.5)	10 (27.8)	
≥10	34 (33.0)	41(26.5)		10 (29.4)	12 (33.3)	
Marital status						
Married	652 (90.4)	1682 (89.5)	<0.01	246 (70.5)	716 (79.8)	<0.01
Single	67 (9.3)	159 (8.5)		101 (28.9)	168 (18.7)	
Missing	2 (0.3)	37 (2.0)		2 (0.6)	13 (1.5)	
Education level						
Middle School or less	228 (31.6)	250 (13.3)	<0.01	178 (51.0)	146 (16.3)	<0.01
High school	295 (40.9)	498 (26.5)		110 (31.5)	365 (40.7)	
College or more	198 (27.5)	1026 (54.6)		61 (17.5)	333 (37.1)	
Missing	0 (0.0)	104 (5.6)		0 (0.0)	53 (5.9)	
Household income (10 ⁴ Korean won/mo)						
<200	291 (41.0)	348 (18.5)	<0.01	130 (38.5)	212 (23.6)	<0.01
200-400	262 (36.9)	728 (38.8)		137 (40.5)	314 (35.0)	
>400	157 (22.1)	588 (31.3)		71 (21.0)	230 (25.7)	
Missing	0 (0.0)	214 (11.4)		0 (0.0)	141 (15.7)	
Body mass index (kg/m ²)						
<18	12 (1.7)	10 (0.5)	<0.01	9 (2.6)	15 (1.7)	0.02
18-24.9	492 (69.2)	1156 (62.5)		230 (67.1)	651 (74.0)	
≥25	207 (23.5)	673 (36.4)		104 (30.3)	208 (23.6)	
Missing	0 (0.0)	10 (0.5)		0 (0.0)	6 (0.7)	
Smoking status						
Non-smoker	166 (23.0)	393 (20.9)	0.47	310 (88.8)	857 (95.5)	<0.01
Ex-smoker	351 (48.7)	953 (50.7)		16 (4.6)	21 (2.4)	
Current smoker	204 (28.3)	532 (28.3)		23 (6.6)	18 (2.0)	
Missing	0 (0.0)	0 (0.0)		0 (0.0)	1 (0.1)	
Alcohol consumption						
Non-drinker	124 (17.2)	308 (16.4)	<0.01	209 (59.9)	569 (63.4)	0.16
Ex-drinker	116 (16.1)	202 (10.8)		28 (8.0)	44 (4.9)	
Current drinker	481 (66.7)	1364 (72.6)		112 (32.1)	283 (31.6)	
Missing	0 (0.0)	4 (0.2)		0 (0.0)	1 (0.1)	
Overcooked meat consumption						
Never	205 (28.4)	928 (49.4)	<0.01	147 (42.1)	577 (64.3)	<0.01
Sometimes	424 (58.8)	774 (41.2)		183 (52.4)	269 (30.0)	
Always	92 (12.8)	168 (9.0)		19 (5.4)	46 (5.1)	
Missing	0 (0.0)	8 (0.4)		0 (0.0)	5 (0.6)	

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Table 1. Continued from the previous page

	Men (n = 2599)			Women (n = 1246)		
	Colorectal cancer (n = 721)	Control (n = 1878)	p-value ¹	Colorectal cancer (n = 349)	Control (n = 897)	p-value ¹
Regular exercise						
No	457 (63.4)	788 (42.0)	<0.01	272 (77.9)	404 (45.0)	<0.01
Yes	264 (36.6)	1076 (57.3)		77 (22.1)	490 (54.7)	
Missing	0 (0.0)	14 (0.7)		0 (0.0)	3 (0.3)	
Family history of cancer						
No	455 (63.1)	1017 (54.2)	<0.01	204 (58.4)	448 (50.0)	<0.05
Yes	266 (36.9)	848 (45.1)		144 (41.3)	439 (48.9)	
Missing	0 (0.0)	13 (0.7)		1 (0.3)	10 (1.1)	
Family history of colorectal cancer						
No	650 (90.2)	1770 (94.3)	<0.01	323 (92.5)	819 (91.3)	0.36
Yes	95 (9.8)	95 (5.0)		25 (7.2)	68 (7.6)	
Missing	0 (0.0)	13 (0.7)		0 (0.3)	10 (1.1)	

Values are presented as number (%).

¹t-test for continuous variables and Pearson chi-square test for categorical variables.

Table 2. Odds ratios (ORs) and 95% confidence intervals (CIs) of overall and sub-sites of colorectal cancer risk in relation to history of diabetes mellitus (DM)

Site (for cases)	Men (n = 2599)				Women (n = 1196)			
	No. of participants	No. of DM (%)	Age-adjusted OR ² (95% CI)	Multivariate ¹ OR ² (95% CI)	No. of participants	No. of DM (%)	Age-adjusted OR ² (95% CI)	Multivariate ¹ OR ² (95% CI)
Controls	1878	184 (9.8)	1.00 (reference)	1.00 (reference)	897	53 (5.9)	1.00 (reference)	1.00 (reference)
Cases								
Overall	721	113 (15.7)	1.47 (1.13, 1.90)	1.53 (1.16, 2.01)	349	40 (11.5)	1.92 (1.24, 2.98)	1.95 (1.20, 3.17)
Proximal	137	21 (15.3)	1.44 (0.88, 2.37)	1.50 (0.90, 2.50)	77	8 (10.4)	1.59 (0.72, 3.52)	1.74 (0.76, 4.00)
Distal	210	43 (20.5)	2.02 (1.39, 2.95)	2.06 (1.40, 3.04)	129	15 (11.6)	2.02 (1.09, 3.74)	1.97 (1.03, 3.79)
Rectum	374	49 (13.1)	1.19 (0.84, 1.68)	1.25 (0.87, 1.79)	143	17 (11.9)	2.04 (1.13, 3.67)	2.02 (1.07, 3.82)

¹Adjusted for age, body mass index, alcohol consumption, overcooked meat consumption and physical activity.

²OR estimates for overall colorectal cancer by binary logistic regression and subsite specific colorectal cancer by polytomous logistic regression.

Table 3. Odds ratios (ORs) and 95% confidence intervals (CIs) of overall colorectal cancer (CRC) risk in relation to duration of diabetes mellitus (DM)

	No DM		DM (< 10 y)		DM (≥ 10 y)	
	No. of CRC/Controls	Multivariate ¹ OR ² (95% CI)	No. of CRC/Controls	Multivariate ¹ OR ² (95% CI)	No. of CRC/Controls	Multivariate ¹ OR ² (95% CI)
Men	608/1694	1.00 (reference)	69/114	1.63 (1.16, 2.23)	34/41	1.64 (0.98, 2.73)
Women	309/844	1.00 (reference)	24/24	2.31 (1.21, 4.39)	10/12	1.87 (0.70, 4.98)

¹Adjusted for age, body mass index, alcohol consumption, overcooked meat consumption and physical activity.

²Binary logistic regression was used for analyses.

In the sub-site analyses, diabetes was associated with increased risk of distal colon cancer in men. In women, diabetes was associated with increased risk of distal colon cancer and rectal cancer. Although the point estimates of proximal colon cancer were similar to those of distal colon cancer, the results were not statistically significant in either men or women. Pre-

vious studies have also found sub-site differences, although the findings have not been consistent. A large population-based cohort study of postmenopausal women found a positive association between diabetes and proximal colon cancer risk, but not distal colon or rectal cancer risk [29]. Another large population-based retrospective cohort study found that

diabetes was positively associated with proximal and distal colon cancer in men and with proximal and rectal cancer in women [30]. In addition to DM, some studies have found other risk factors that differentially affect CRC risk by sub-site [31-33]. It has been suggested that a biological differences could be present among sub-sites. Some possible biological mechanisms may explain this relationship. First, embryological differences may affect the susceptibility of colorectal sub-sites to carcinogens; the area extending from the cecum to the proximal two thirds of the transverse colon originates from the midgut and the rest originates from the hindgut [34,35]. Second, differences in tumor methylation status, BRAF and KRAS mutation status, and DNA microsatellite instability may be associated with sub-site differences. Specifically, proximal tumors appear to be related to CpG island methylator phenotype (CIMP)-high and BRAF-mutated tumors, while distal tumors have been found to be mostly related to no-CIMP and microsatellite-stable tumors; additionally, tumors in the cecum appear to show a high frequency of KRAS mutations [36].

Our study has some limitations. First, because the control subjects were participants in a health screening program in Korea [37], the health-related behavior of the control subjects may have differed from that of the case subjects. Kim et al. [38] investigated the factors associated with participants attending a national cancer screening program in Korea and found that behavior, attitudes, and subject norms had important effects on participant intentions. Moreover, the DM status of the controls may have been underestimated. According to the 2012 annual report of the National Health Screening Program of Korea, the self-reported prevalence rates of DM among subjects between 40 and 60 years of age and more than 60 years of age were 7.04% and 13.11%, respectively [39]. However, according to the fourth Korea National Health and Nutrition Examination Survey, the corresponding prevalence rates of DM were 9.85% and 17.21% in 2007 to 2009, respectively [2]. Since the controls were recruited from participants in a health screening program, the association between DM and CRC risk may have been overestimated. Second, the control subjects were only tested with the fecal occult blood test, which is a screening test for CRC; thus, CRC cases could have been misclassified. However, this is a relatively unlikely possibility because CRC is a rare disease. In addition, controls with colon polyps may have been included in this study. However, since colorectal polyps have risk factors similar to those associated with colorectal cancer, this misclassification would have skewed the results toward

the null. Third, when we analyzed CRC risk in relation to the duration of DM, women with a duration of DM of less than 10 years exhibited the highest adjusted OR. This may have been due to surveillance bias or screening bias; CRC patients might have sought medical service more recently, and therefore they might have been more likely to be diagnosed with DM. Finally, because we used self-reported DM history, memory bias or recall bias leading to the misclassification of DM status may have affected our results. However, a validation study of self-reported DM history conducted in Japan supported its reliability [40].

In summary, in this study, we observed that DM was associated with an increased risk of CRC in Koreans. Due to the case-control study design, which is vulnerable to selection bias in a control group that was recruited from healthy individuals who participated in a national health screening program, the association could have been overestimated.

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CONFLICT OF INTEREST

The authors have no conflicts of interest associated with the material presented in this paper.

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